

Docket No.: 2294-0122PUS1  
(Patent)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Patent Application of:

Alfonso ROMERO et al.

Application No.: 10/594,004

Confirmation No.: 8959

Filed: September 25, 2006

Art Unit: 1616

For: PROLONGED-RELEASE COMPOSITIONS  
COMPRISING TORASEMIDE AND A  
MATRIX-FORMING POLYMER

Examiner: Abigail Fisher

**DECLARATION UNDER 37 CFR 1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, Antonio GUGLIETTA, declare and say as follows:

I am an inventor in the present application and I am familiar with U.S. Application No. 10/594,004.

The experiments discussed herein were conducted under my supervision and control.

The following test data shows that the inherent crystallinity of the Torasemide [e.g. in the tablets of Examples 6-9 of the present application] is not affected by the process used to make the tablet.

**Discussion****Aim**

The aim of this study is to verify the crystallinity of Torasemide (drug substance) in the tablets of Examples 6-9 of US patent application No. 10/594,004.

The tablets of Example 9 correspond to the commercial drug product (Sutrilneo). Torasemide is produced in the polymorphic form I.

The morphology of Torasemide in the pill was characterised using X-Ray Powder Diffraction (XRPD).

**Experimental**

Four samples were provided to the XRPD group from the Scientific-Technical Service of the University of Barcelona (SCT-UB). These samples were:

- PILL Torasemide: commercial pill Sutrilneo 5 mg, batch E009. It was broken carefully with a metallic spatula for the analysis.
- MIX Torasemide: the same composition of the PILL Torasemide (see Table 1) prepared in the laboratory.
- MIX Placebo: same mixture as MIX Torasemide, but without Torasemide.
- API Torasemide: the drug substance, batch: 1E0419.

The pill composition, drug substance and excipients used for the preparation of the MIX Torasemide and MIX placebo samples are summarised in Table 1.

Table 1. Torasemide pill composition.

Compound	Batch	Amount (mg)
Torasemide	1E0419	20
Lactose	0H0636	180.6
Meyprogat 90	1E0398	13.6
Corn starch	1E0459	123.08
Aerosil 200	9K0826	1.70
Magnesium stearate	0E0415	1.02
Total weight	n.a.	340

These four samples were analysed by XRPD. The results were compared in order to find out whether or not Torasemide was present in the pill in a crystalline form.

The XRPD instrument, procedure and parameters are described in the report provided by the SCT-UB included in the annexes.

### Results and discussions

The results were extracted from the report sent by the SCT-UB. The XRPD diagrams for the samples PILL Torasemide, MIX Torasemide, MIX Placebo and API Torasemide were compared (see figures 1, 2 and 3).

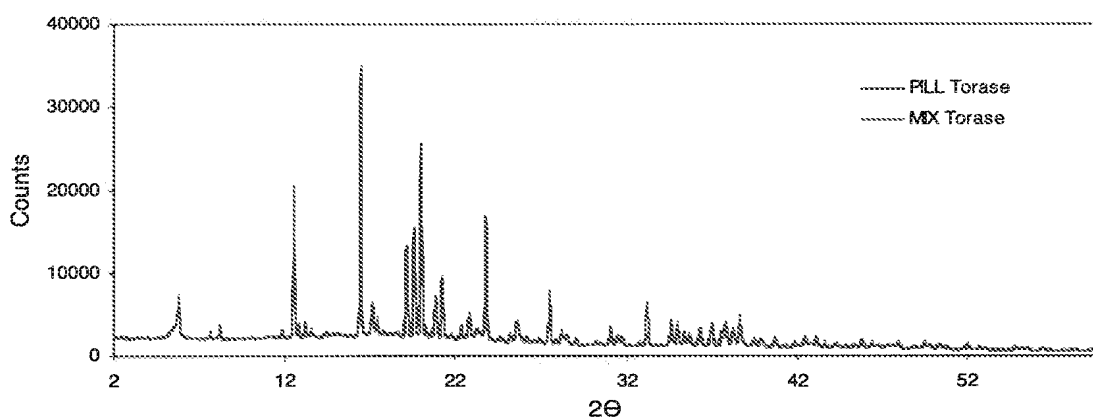


Figure 1. PILL Torasemida and MIX Torasemida diagrams overlaid.

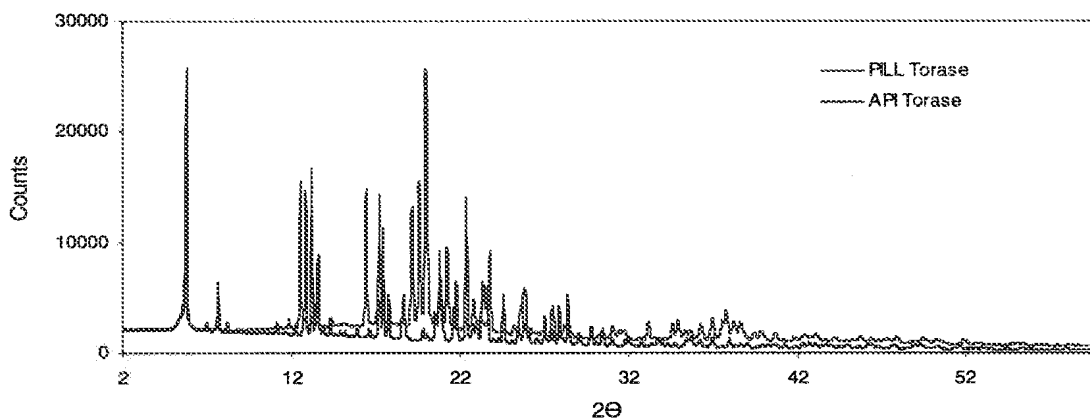


Figure 2. PILL Torasemida and API Torasemida diagrams overlaid.

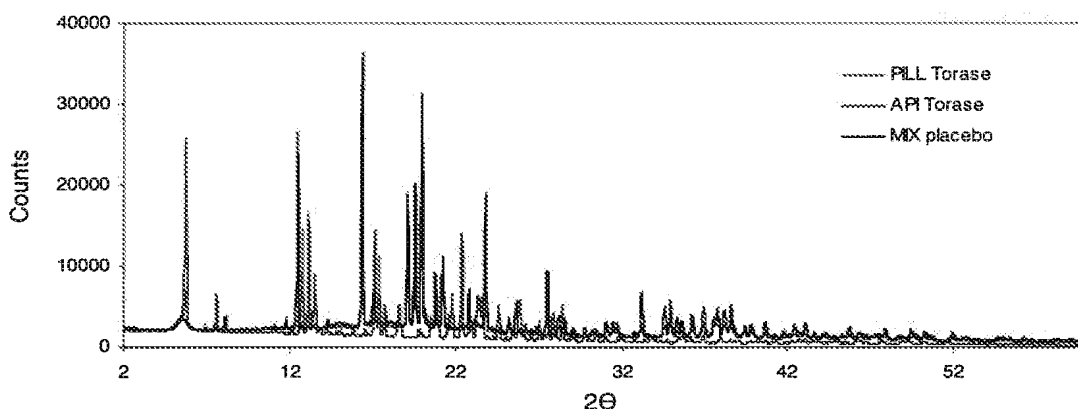


Figure 3. PILL Torasemida, MIX Placebo and API Torasemida diagrams overlaid.

Figure 1 compares the obtained diagrams for the PILL Torasemida and MIX Torasemida samples. The two diagrams show essentially the same patterns. The crystalline phases present in the two samples are the same. Figure 2 compares the obtained diagrams of the samples PILL Torasemida and API Torasemida. The API main peaks are observed also in the pill's diagram. Figure 3 compares the diagrams of PILL Torasemida, API Torasemida and MIX Placebo. The main peaks of the API diagram observed in the pill diagram are not observed in the placebo diagram.

Figures 4 and 5 show some examples of the peaks that appear in the pill and in the API but not in the placebo diagram.

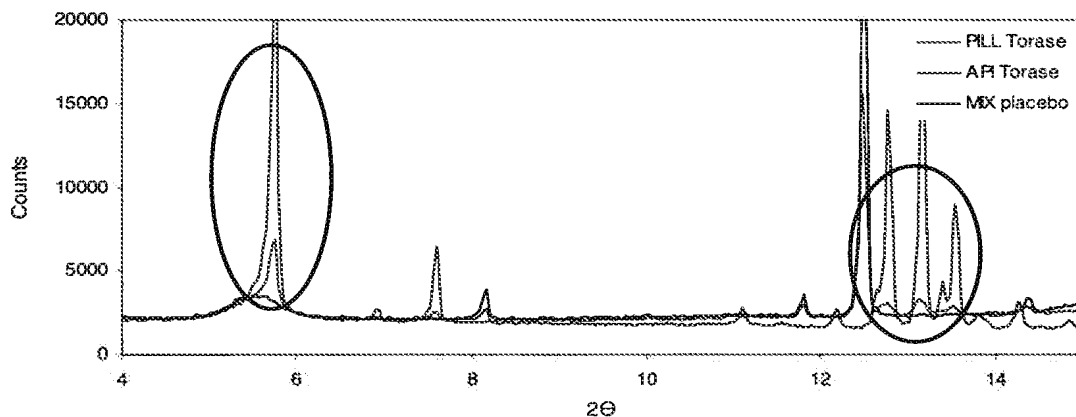


Figure 4. Magnification of the PILL Torasemida, MIX Placebo and API Torasemida diagrams overlaid.

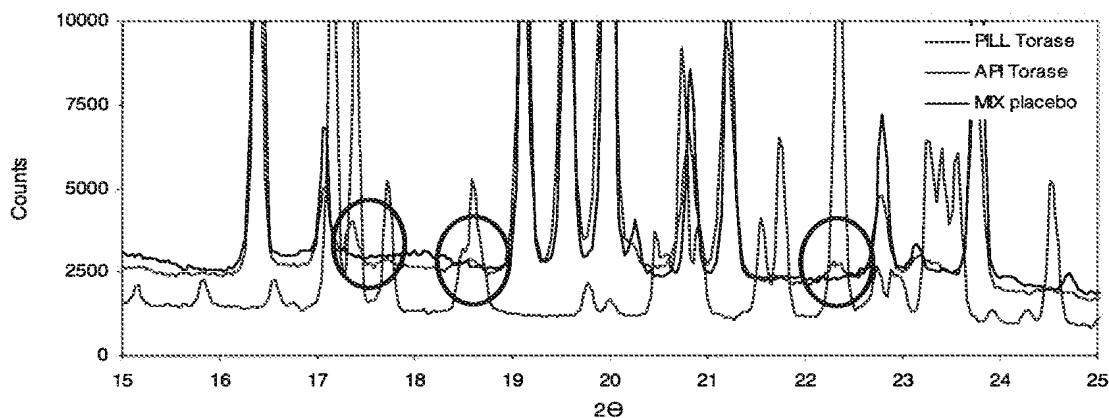


Figure 5. Magnification for the PILL Torasemida, MIX Placebo and API Torasemida diagrams overlaid.

The first circle in figure 4 shows the main peak of Torasemide drug substance, the most intense. This peak appears also in the pill and not in the placebo, indicating the presence of the same crystalline form in the API and in the pill. The second circle is marking a triplet present in the Torasemide drug substance diagram and in the pill, at less intensity, and missing in the placebo. Figure 5 shows the magnification of several peaks that appear in Torasemide drug substance and in the pill, at less intensity.

Figure 6 is a magnification of the diagrams overlaid for the pill, the laboratory mixture and the API. The pill and the laboratory mixture diagrams show some differences in peak intensity. Comparing with the API's diagram it was observable that the peaks showing higher differences were from the excipients and were not detected in the API's diagram. The rest of peaks presented in the pill and the laboratory mixture were comparable; therefore, the level of Torasemide's crystallinity in the pill was substantially the same as observed in the laboratory mixture, prepared with the crystalline API.

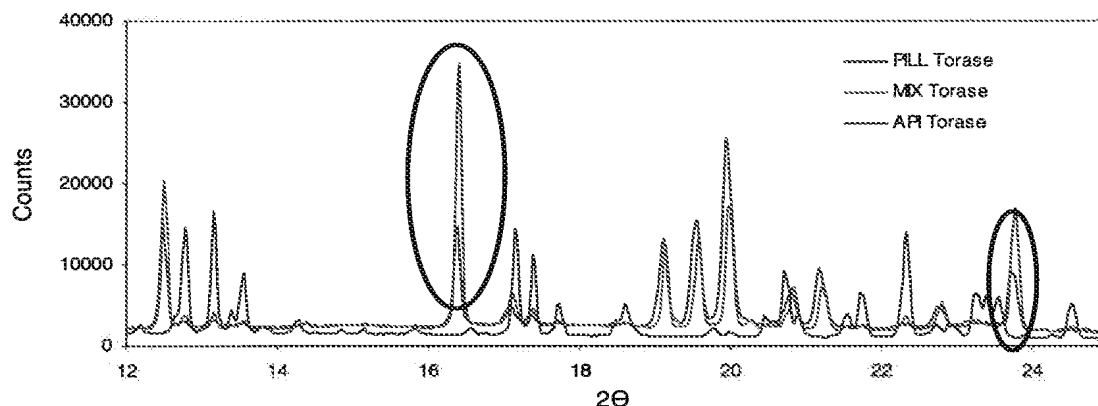


Figure 6. Magnification for the PILL Torasemida, MIX Torasemida and API Torasemida diagrams overlaid. Circled

It is demonstrated that the Torasemide drug substance contained in the pill Sutrilneo 5 mg is crystalline, and it has the same crystalline form than the Torasemide drug substance (batch: 1E0419).

The results from the XRPD analyses makes it unnecessary to perform additional DSC analyses, as the protocol states.

## Conclusions

From the XRPD results, it can be concluded that the crystalline form of the Torasemide contained in the pill Sutrilneo 5 mg (batch E009) corresponds to the polymorph form I, the same as for the Torasemide drug substance (batch: 1E0419). More specifically, our data shows that the Torasemide used in the invention is inherently crystalline. Accordingly, it is clear that the active ingredient in the tablets of Examples 6-9 is still in crystalline form and not destroyed by the process of making the tablets in the Examples. As such, the present compositions [e.g. in the tablets of Examples 6-9] are crystalline, which is distinct from US 2003/0153608A1 to Maegerlein et al., which teaches compositions comprising torasemide in “essentially noncrystalline form.”

## ANNEXES

## Annex 1. Final report provided by the SCT-UB.



PNT 2090143 DOC/006 Ed. 9. Annex VII

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REGISTRY Num. 03953/2011

Mr. Jaume SEUMA  
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C/ Joan de Sada, 32  
08028 Barcelona

## Analysed samples

Description:	Four powder solid samples related to the pharmaceutical product <i>Toraseמיד</i>	
References	User	DRX
	<i>MIX Toraseמיד</i>	03953/2011-1
	<i>MIX Placebo</i>	03953/2011-2
	<i>PILL Toraseמיד</i>	03953/2011-3
	<i>API Toraseמיד</i>	03953/2011-4
Performed experiments:	X-ray powder diffraction analysis	
Date of sample reception:	11-X-2011	
Date of the experiments:	18-X-2011	

## Methodology

Sample preparation:

The samples were sandwiched between polyamide (*Kapton*) films of 15 microns of thickness.

Instrument and experimental conditions:

*PANalytical X'Pert PRO MPD  $\theta/\theta$*  powder diffractometer of 240 millimetres of radius, in a configuration of convergent beam with a focalizing mirror and a transmission geometry with flat samples sandwiched between low absorbing films  
Cu K $\alpha$  radiation ( $\lambda = 1.5418 \text{ \AA}$ ).  
Work power: 45 kV – 40 mA.  
Incident beam slits defining a beam height of 0.4 millimetres  
Incident and diffracted beam 0.02 radians *Soller* slits  
*PIXcel* detector: Active length = 3.347".  
2 $\theta$  scans from 2 to 60  $^{\circ}2\theta$  with a step size of 0.026  $^{\circ}2\theta$  and a measuring time of 200 seconds per step



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### Objectives

The sample *API Torasemida* is a powder sample of the API pharmaceutical product *Torasemide*. The sample *PILL Torasemida* is a pharmaceutical speciality, a pill, containing a 5 % in weight of the API pharmaceutical product *Torasemide*. The sample *MLX Torasemide* is a powder mixture with the same components than in the pill pharmaceutical speciality. The sample *MIX Placebo* is a powder mixture with the same components than in the pill pharmaceutical speciality but without the API pharmaceutical product *Torasemide*.

The objective of the study is to determine if the API pharmaceutical product *Torasemide* in the pill pharmaceutical speciality *PILL Torasemida* is or not crystalline and in the case of being crystalline determine if the crystalline form is or not the same than the one in the powder sample of the API pharmaceutical product.

### Results

Figure 1, 2, 3 and 4 depict the obtained X-ray powder diffraction diagrams in the main angular range from 2 to 40 °2θ.

Figure 5 compares the obtained diagrams of the samples *PILL Torasemida* and *MLX Torasemida*. The two diagrams are essentially the same. The crystalline phases present in the two samples are the same. Figure 6 compares the obtained diagrams of the samples *PILL Torasemida* and *API Torasemida*. All the main peaks in the *API Torasemida* sample diagram are observed in the *PILL Torasemida* sample diagram. Figure 7 compares the diagrams of the samples *PILL Torasemida*, *API Torasemida* and *MLX Placebo*. The main peaks of the *API Torasemida* sample diagram observed in the *PILL Torasemida* sample diagram are not observed in the *MIX Placebo* sample diagram. It is clear that the API pharmaceutical product *Torasemide* in the pill pharmaceutical speciality *PILL Torasemida* is crystalline and that the crystalline form is the same than the one in the powder sample of the API pharmaceutical product.



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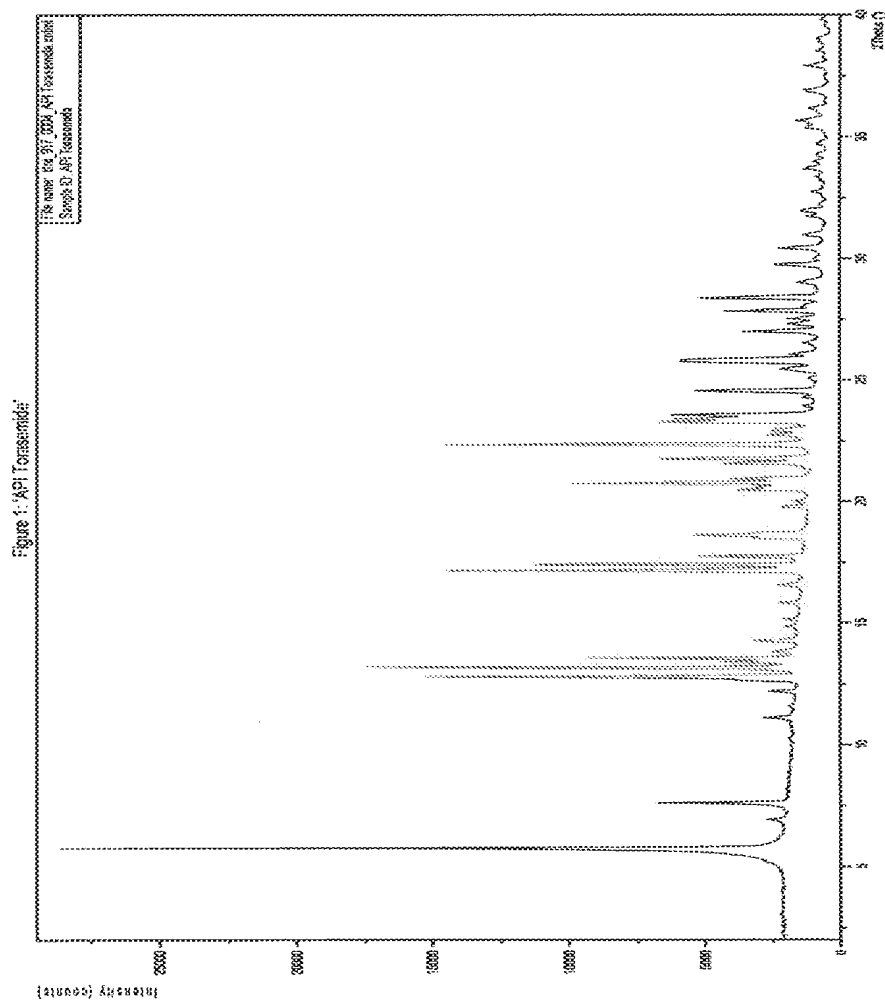


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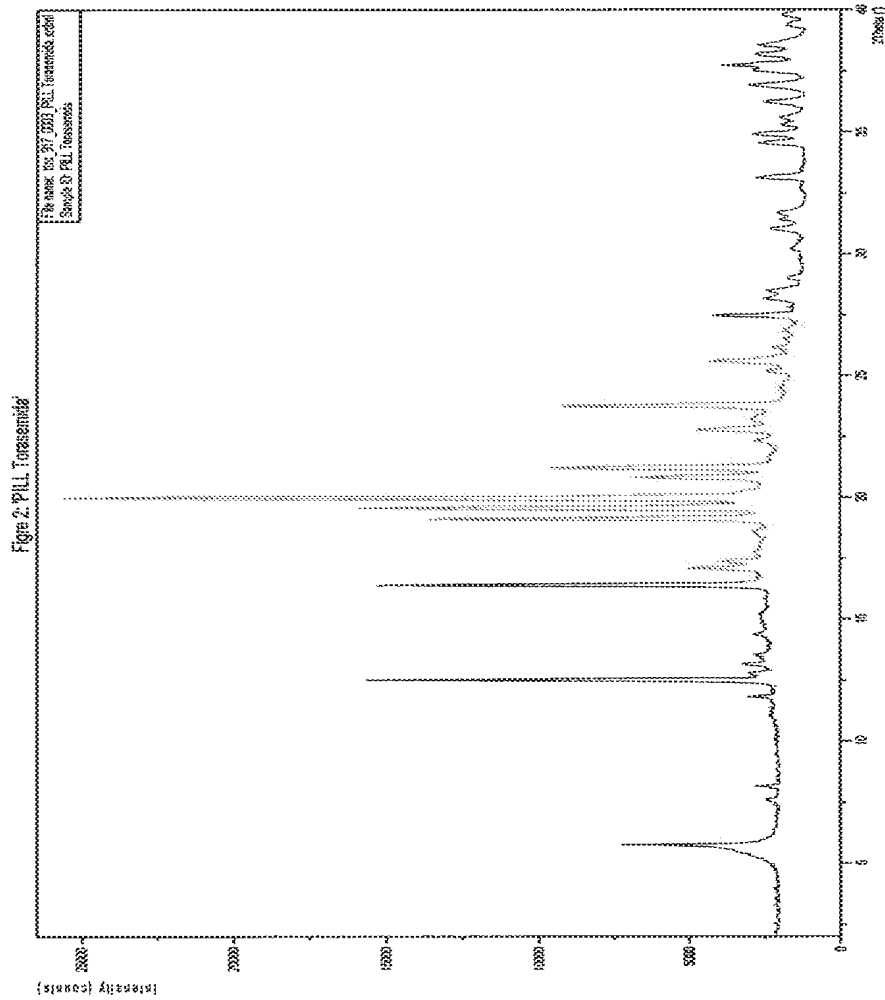
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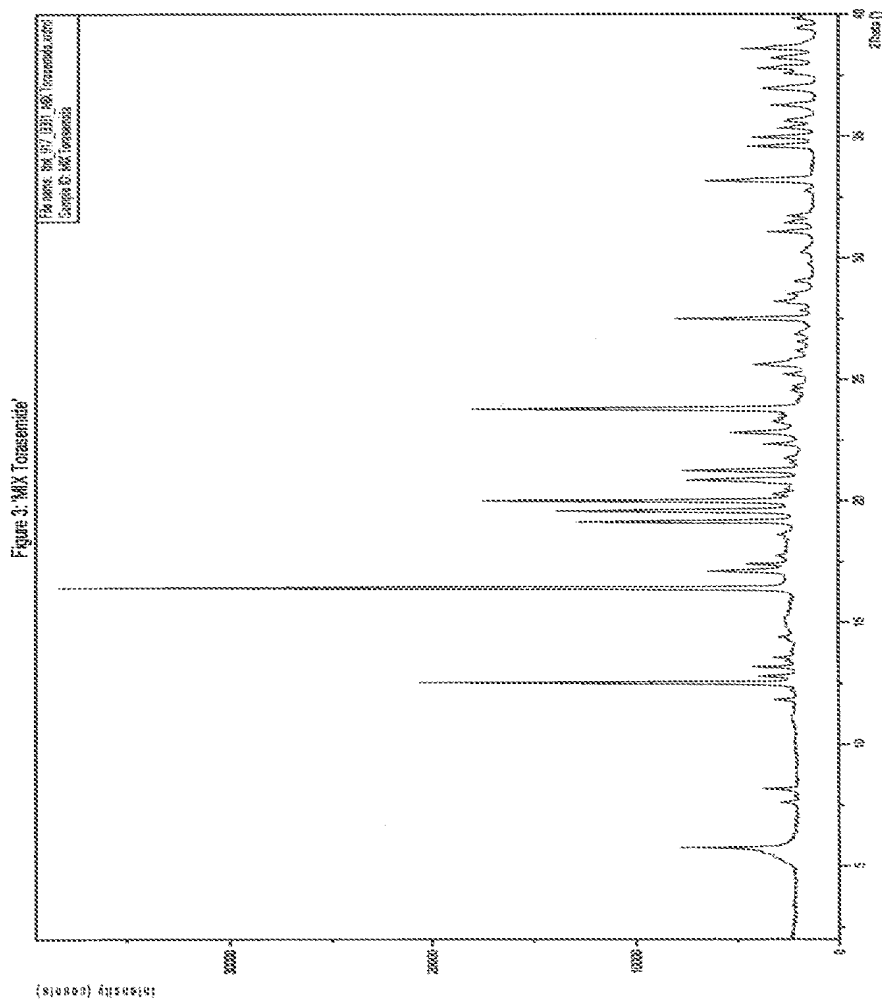


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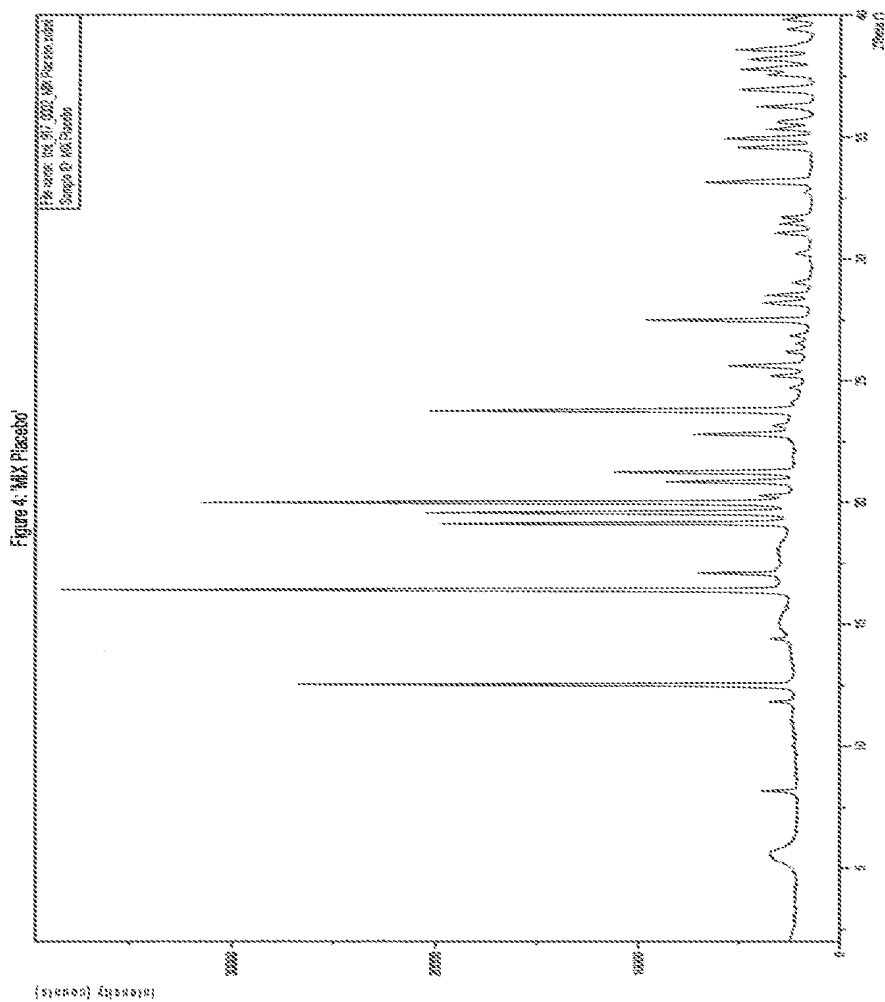
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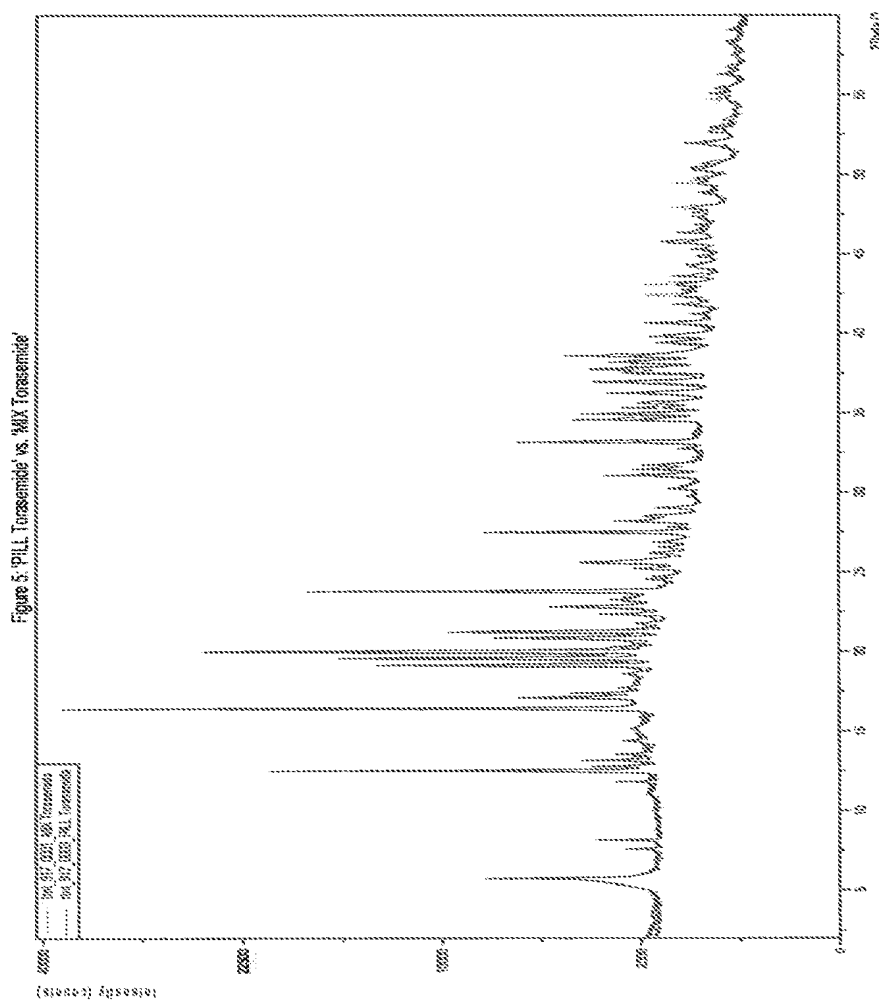
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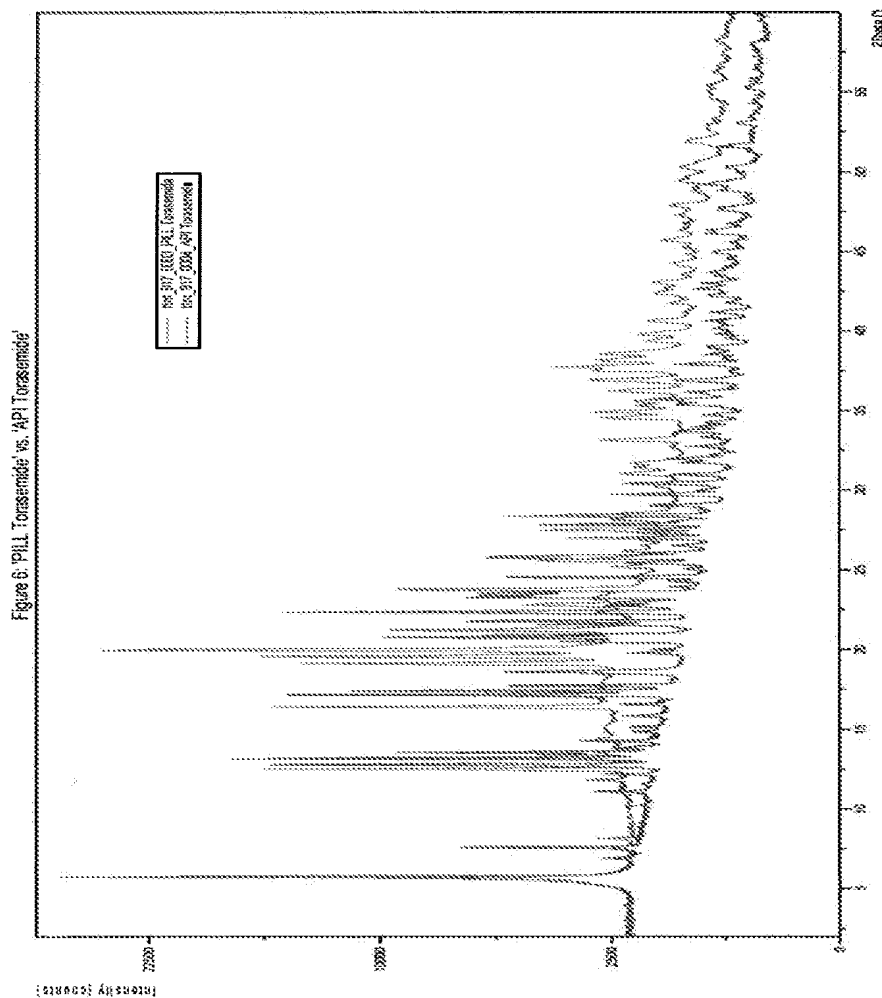
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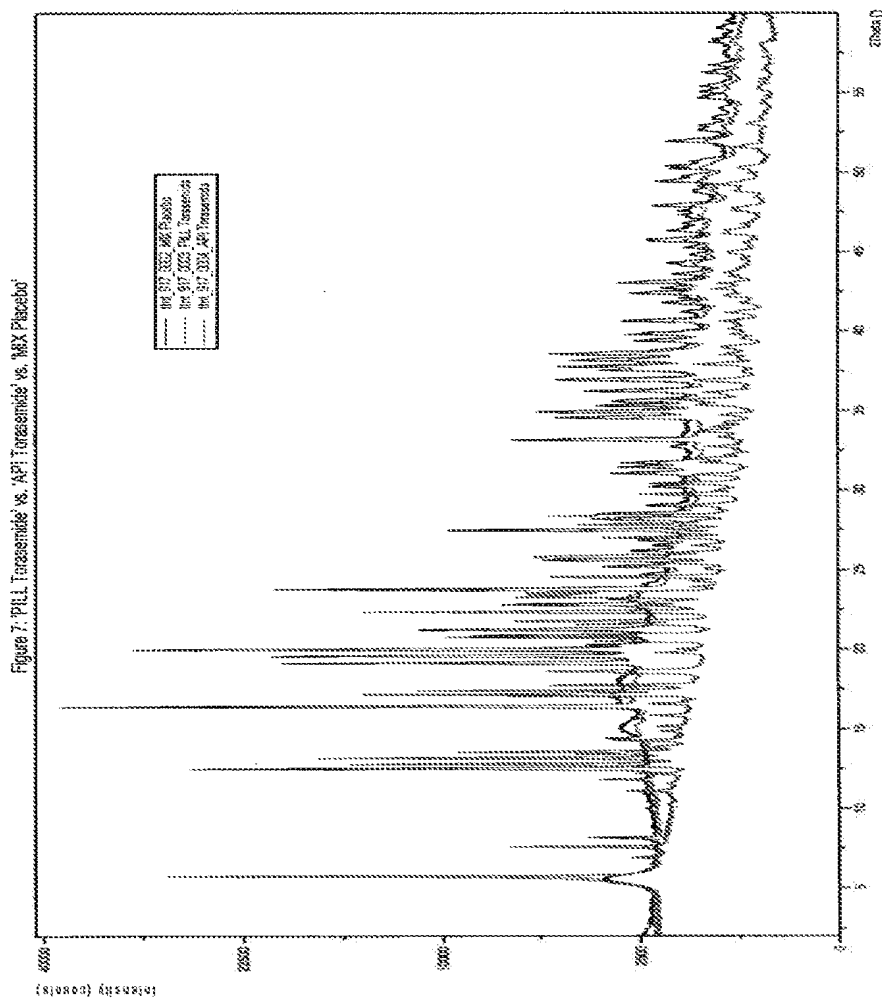
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Pàg. 10/10

Barcelona, 31<sup>st</sup> October 2011

Dr. Xavier Alcobé Ollé  
Head of the X-ray Diffraction Department

- The results refer only to the samples analysed.
- This report cannot be reproduced partially without prior written consent by the Scientific-Technical Services.
- The samples will be kept for a period of three months after releasing this report, and will be destroyed thereafter. The primary results will be kept for five years.
- The Scientific-Technical Services has a Quality Management System certified in accordance with the standard ISO 9001 by APPLUS.



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## Annex 2. Certificate of Analysis of Torasemide (see table 1).



Ferrer Internacional S.A.  
Planta Especialidades Farmacéuticas  
Joan Buscaà 1-8  
08173 Sant Cugat del Valès  
Barcelona - España / Spain

## Certificate of analysis

Material:	MICROCRYSTALLINE TORASEMIDE		
Material code:	3003379	Batch:	1E0419
Amount:	60000,000 G	Supplier:	MEDA AB
		Supplier batch:	MH10065006
		Manufacturing date:	04-2010
		Retest date:	04-2013

Components	Result	Requirements
ANALYTIC CERTIFICATE RECEPTION	PASS	CERTIFICATE RECEIVED

Analysis date: 18-05-2011

Specification: 3003379 (N) TORASEMIDA MICROCRIST. (gen/ver: 1/1)

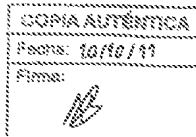
Status: COMPLIES

Responsible: Montse Planells

Electronically generated certificate, valid without signature

Complies Ph. Eur. requirements

Certificado\_estrup\_FISA\_nt.rep / 20101214



Original a: CPD

Page 1 of 1



Ferrer Internacional S.A.  
Planta Especialidades Farmacéuticas  
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08173 Sant Cugat del Valles  
Barcelona - España / Spain

## Certificate of analysis

Material:	MICROCRYSTALLINE TORASEMIDE		
Material code:	3003379	Batch:	1D0327
Amount:	60000,000 G	Supplier:	ROCHE DIAGNOSTICS
		Supplier batch:	MH10085006
		Manufacturing date:	04-2010
		Retest date:	04-2013

Components	Result	Requirements
PHYSICAL-CHEMICAL CONTROL		
APPEARANCE	PASS	WHITE OR ALMOST WHITE POWDER
IDENTIFICATION		
IR IDENTIFICATION	POSITIVE	RESPECT STANDARD BY IR
X RAYS IDENTIFICATION	POSITIVE	POLYMORPHIC FORM I
TESTS		
HEAVY METALS	PASS	<=10 (ppm)
SULPHATED ASH	0	<=0.1 (%)
LOSS ON DRYING	1	<=0.5 (%)
PARTICLE SIZE		
PARTICLE SIZE <12 µm	PASS	>=50 (%)
PARTICLE SIZE <24 µm	PASS	>=90 (%)
PARTICLE SIZE <48 µm	PASS	>=99 (%)
SUSTANCIA RELACIONADAS (HPLC)		
IMPURITY A	<0.05	<= 0.1 (%)
IMPURITY B	0.2	<= 0.5 (%)
IMPURITY C	0.1	<= 0.1 (%)
IMPURITY D	NOT DETECTED	<= 0.1 (%)
ANY OTHER IMPURITY	<0.05	<=0.1 (%)
TOTAL IMPURITIES	0.3	<=0.6 (%)
ASSAY		
POTENTIOMETRIC TITRATION (ANHYDROUS)	101.0	99.0 - 101.0 (ANHYDROUS SUBSTANCE) (%)
TRIETHYLAMINE (CE)		
TRIETHYLAMINE	<320	<=320 (ppm)

Analysis date: 03-05-2011

Specification: 3003379 TORASEMIDE MICROCRISTALINA (gen/ver: 13/1)

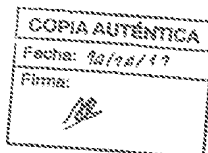
Status: COMPLET

Responsible: Montse Planells

Electronically generated certificate, valid without signature

Complies Ph. Eur. requirements

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Page 1 of 1

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11 NOV 2009 10:51 ROCHE BASEL PTLC +41 61 6853036 NR. 7046



Safety Data Sheet		Torasemide	
<b>1. Product and Company Identification</b>			
Product name	Torasemide		
Product code	04 7523 B		
Company information	Enquiries: F. Hoffmann-L. Roche AG Postfach CH-4070 Basel Switzerland	Local representation:	
	Phone	+41-61/688 54 80	
	Fax	+41-61/681 72 76	
<b>2. Composition/Information on Ingredients</b>			
Characterization	pharmaceutical active substance		
Chemical name	- N-[[[1-Methylethylamino]carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonyl]-2-methyl-2-propanesulfonamide		
CAS number	55211-40-6		
Empirical formula	C <sub>21</sub> H <sub>26</sub> N <sub>4</sub> O <sub>5</sub> S		
Molecular mass	348.46 g/mol		
<b>3. Hazards Identification</b>			
Most important hazards	- No particular hazards known.		
<b>4. First-aid measures</b>			
Eye contact	- rinse immediately with tap water for 10 minutes - open eyelids forcibly - consult physician		
Skin contact	- remove contaminated clothes, wash affected skin with water and soap - do not use any solvents		
Inhalation	- remove the casualty to fresh air and keep him/her calm - consult physician		
Note to physician	- treat symptomatically		

Date: 17.4.00/CEE (SEIMO)

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Page: 1/3

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## Terasemide

**5. Fire-fighting measures**

- |                                |  |
|--------------------------------|--|
| Suitable extinguishing media   | - water spray jet, dry powder, foam, carbon dioxide  |
| Unsuitable extinguishing media | - full water jet   |
| Specific hazards               | - formation of toxic and corrosive combustion gases (nitrogen oxides, sulfur oxides) possible<br>- Material is combustible |
| Protection of fire-fighters    | - precipitate gases/vapours/mists with water spray<br>- use self-contained breathing apparatus                             |

**6. Accidental release measures**

- |                          |   |
|--------------------------|---|
| Personal precautions     | - evacuate area, remove sources of ignition, ventilate                            |
| Environmental protection | - do not allow to enter drains or waterways<br>- avoid release to the environment |
| Methods for cleaning up  | - collect solids (avoid dust formation) and hand over to waste removal            |

**7. Handling and storage****Handling**

- |                    |   |
|--------------------|---|
| Technical measures | - processing in closed systems, if possible superposed by inert gas (e.g. nitrogen)<br>- take precautionary measures against electrostatic charging<br>- avoid dust formation |
| Suitable materials | - stainless steel, glass, aluminium, enamel   |

**Storage**

- |                     |   |
|---------------------|---|
| Storage conditions  | - no special measures or restrictions for storage known |
| Packaging materials | - tightly closing                                       |

**8. Exposure controls/Personal protection**

- |                      |          |
|----------------------|----------|
| Engineering Measures | - see 7. |
|----------------------|----------|

**Personal protective equipment**

- |                        |  |
|------------------------|--|
| Respiratory protection | - in case of open handling or accidental release:<br>particle mask or respirator with independent air supply |
| Hand protection        | - protective gloves  |
| Eye protection         | - safety glasses   |

16.11.01 VIE 18:18 FAX -33 833302376 GRUP FERRER COMPRAS --- FABRICA 92004  
16 NOV 2001 13:41 ROCHE BASEL PTLC +41 61 6883019 NA 7148 5. 4

## Fossemide

**9. Physical and chemical properties**

Colour white  
Form solid  
Odour odourless  
Solubility badly soluble, water  
Melting temperature 157 to 164 °C

**10. Stability and reactivity**

Stability - stable under the conditions mentioned in chapter 7

**11. Toxicological information**

Acute toxicity - LD<sub>50</sub> > 5'000 mg/kg (oral, rat)  
- LD<sub>50</sub> > 500 mg/kg (i.v., rat)  
Note - diuretic

**12. Ecological information**

Air pollution - observe local/national regulations  
Note - no ecotoxicological data available on this compound

**13. Disposal considerations**

Waste from residues - observe local/national regulations regarding waste disposal  
- incinerate in qualified installation with flue gas scrubbing

**14. Transport information**

Note - not classified by transport regulations

**15. Regulatory information**

Note - no classification and labelling according to EU  
Water hazard class (Germany) 2: hazardous for water (own classification according to directive VwVwG of 17.06.1999)

**16. Other information**

Edition documentation first edition

The information in this safety data sheet is based on current scientific knowledge. It should not be taken as expressing or implying any warranty concerning product characteristics.

## Annex 3. Certificate of Analysis of Aerosil 200 (see table 1).



Ferrer Internacional S.A.  
Planta Especialidades Farmacéuticas  
Joan Brucella 1-6  
08173 Sant Cugat del Valles  
Barcelona - España / Spain

## Certificado de análisis

Producto:	AEROSIL 200		
Código producto:	3000021	Lote:	9K0826
Cantidad:	450000,000 G	Proveedor:	IMPEX QUIMICA S.A.
		Lote proveedor:	3150091614
		Fecha fabricación:	11-2009
		Fecha retest:	12-2012

Determinaciones	Resultado	Especificaciones
CONTROL FISICO-QUIMICO		
ASPECTO	CONFORME	POLVO BLANCO O CASI BLANCO, LIGERO, FINO Y AMORFO
IDENTIFICACION SILICATOS	POSITIVA	SATISFACE REACCION SILICATOS
ENSAYOS		
pH (USP)	4.7	3.5 - 5.5
pH (Ph. Eur.)	4.5	3.5 - 5.5
CLORUROS	CONFORME	<=250 (ppm)
METALES PESADOS	CONFORME	<=25 (ppm)
PERDIDA POR DESECACION (USP)	32	<= 2.5 (%)
PERDIDA POR CALCINACION (USP)	78	<= 2.0 (%)
PERDIDA POR CALCINACION (Ph. Eur.)	43	<= 5.0 (%)
ARSENICO (USP)	CONFORME	<= 8
VALORACION (GRAVIMETRICA)		
OXIDO DE SILICE (Ph. Eur.)	99.5	99.0 - 100.5 (spc.) (%)
OXIDO DE SILICE (USP)	98.9	99.0 - 100.5 (spc.) (%)

Fecha análisis: 04-12-2009

Especificación: 3000021 AEROSIL 200 (gen/ver. 8/1)

Dictamen: CONFORME

Nº Certificado: 700346525 / 4

Certificado emitido electrónicamente, es válido sin firma

Cumple requerimientos de Ph. Eur. y USP

Certificado\_mmpa\_FISA\_mf rep / 20091201

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## Annex 4. Certificate of Analysis of Corn starch (see table 1).



Ferrer Internacional S.A.  
Planta Especialidades Farmacéuticas  
Joan Brucada 1-9  
08173 Sant Cugat del Valles  
Barcelona - España / Spain

## Certificado de análisis

Producto:	ALMIDON DE MAIZ		
Código producto:	3000031	Lote:	1E0459
Cantidad:	100000,000 G	Proveedor:	BRENTAS QUIMICA, S.A.
		Lote proveedor:	01257670
		Fabricante:	600146 CERESTAR
		Fecha fabricación:	02-2010
		Fecha retest:	02-2013

Determinaciones	Resultado	Especificaciones
CONTROL FISICO-QUIMICO		
ASPECTO	CONFORME	POLVO MUY FINO, BLANCO O AMARILLENTO
IDENTIFICACION MICROSCOPICA	POSITIVA	PASA TEST
IDENTIFICACION POR CALENTAMIENTO	POSITIVA	PASA TEST
IDENTIFICACION CON IODO	POSITIVA	COLORACION VIOLETA-AZUL
ENSAYOS		
pH	5.4	4.0 - 7.0
ELEMENTOS EXTRAÑOS	CONFORME	PASA TEST
SUSTANCIAS OXIDANTES	CONFORME	<= 20 ppm
DIOXIDO DE AZUFRE	CONFORME	<= 50 (ppm)
HIERRO	CONFORME	<= 10 (ppm)
PERDIDA DE PESO	11	<= 15.0 (%)
GENIZAS SULFURICAS	.2	<= 0.6 (%)
CONTROL MICROBIOLOGICO		
RECuento MICROBIOS AEROBIOS TOTAL	<10	<= 1 E3 (ufa/g)
RECuento MOHOS Y LEVADURAS TOTAL	<10	<= 1 E2 (ufa/g)
ESCHERICHIA COLI	CONFORME	AUSENCIA EN 1 g
SALMONELLA	CONFORME	AUSENCIA EN 10 g

Fecha análisis:	23-06-2011	Especificación:	3000031 ALMIDON DE MAIZ ( per/ver: 13/1)
Dictamen:	CONFORME		
Responsable:	Monise Planells		

Certificado emitido electrónicamente, es válido sin firma

Cumple requerimientos de Ph. Eur.

Certificado\_nmcq\_FSA\_m1.rep / 20101214

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## Annex 5. Certificate of Analysis of Lactose (see table 1).



Ferrer Internacional S.A.  
Planta Especialidades Farmacéuticas  
Joan Buscà 1-9  
08173 Sant Cugat del Valles  
Barcelona - España / Spain

## Certificado de análisis

Producto:	LACTOSA		
Código producto:	3000263	Lote:	0H0636
Cantidad:	4000000.000 G	Proveedor:	QUIMIDROGA S.A
		Lote proveedor:	10512326
		Fabricante:	600236 DMV
		Fecha fabricación:	04-2010
		Fecha retest:	09-2013

Determinaciones	Resultado	Especificaciones
<b>CONTROL FISICO-QUIMICO</b>		
ASPECTO	CONFORME	POLVO CRISTALINO BLANCO O PRACTICAMENTE BLANCO
IDENTIFICACION IR	POSITIVA	RESPECTO PATRON POR IR
IDENTIFICACION AGUA	POSITIVA	SATISFACE LOS REQUERIMIENTOS DEL ENSAYO DEL AGUA
<b>ENSAYOS</b>		
ASPECTO DE LA SOLUCION	CONFORME	LIMPIDA Y $\leq$ PA7
ACIDEZ O ALCALINIDAD	CONFORME	$\leq$ 0.4 ml NaOH 0.1M
ROTACION ESPECIFICA	55	54.4 - 55.9 (spa) (°)
ABSORCION A 480nm	0.01	$\leq$ 0.04
ABSORCION 210 A 220 nm	0.04	$\leq$ 0.25
ABSORCION 270 a 300 nm	0.01	$\leq$ 0.07
METALES PESADOS	CONFORME	$\leq$ 5 (ppm)
AGUA (K. Fischer)	5.07	4.5 - 5.5 (%)
CENIZAS SULFURICAS	.03	$\leq$ 0.1 (%)
<b>CONTROL MICROBIOLOGICO</b>		
RECuento MICROBIOS AEROBIOS TOTALES	$<10$	$\leq$ 1 E2 (ufc/g)
ESCHERICHIA COLI	CONFORME	AUSENCIA EN 1 g

Fecha análisis: 13-09-2010

Especificación: 3000263 LACTOSA (gen/ver: 5/1)

Dictamen: CONFORME

Nº Certificado: 790053502 / 1

Certificado emitido electrónicamente, es válido sin firma

Cumple requerimientos de Ph. Eur.

Certificado\_mnpp\_FISA\_ml.rep / 20091201

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## Annex 6. Certificate of Analysis of Magnesium stearate (see table 1).



Ferrer Internacional S.A.  
Planta Especialidades Farmacéuticas  
Juan Boscalle 1-5  
08173 Sant Cugat del Vallès  
Barcelona - España / Spain

## Certificado de análisis

Producto:	ESTEARATO DE MAGNESIO		
Código producto:	3000169	Lote:	0E0415
Cantidad:	450000,000 G	Proveedor:	BRENNTAG QUIMICA,S.A
		Lote proveedor:	C004537
		Fecha fabricación:	03-2009
		Fecha retest:	06-2013

Determinaciones	Resultado	Especificaciones
<b>CONTROL FISICO-QUIMICO</b>		
ASPECTO	CONFORME	POLVO BLANCO LIGERO MUY FINO
IDENTIFICACION CG	POSITIVA	TIEMPO DE RETENCION COINCIDE CON PATRON
IDENTIFICACION DE MAGNESIO	POSITIVA	RESPECTO REACCION QUIMICA
<b>ENSAYOS</b>		
ACIDEZ	0	$\leq 0.05$ (ml NaOH 0.1M)
ALCALINIDAD	0.01	$\leq 0.05$ (ml HCl 0.1M)
CLORUROS (USP)	CONFORME	$\leq 0.1$ (%)
CLORUROS (Ph. Eur.)	CONFORME	$\leq 0.1$ (%)
SULFATOS (USP)	CONFORME	$\leq 1.0$ (%)
SULFATOS (Ph. Eur.)	CONFORME	$\leq 1.0$ (%)
CADMIUM	CONFORME	SE ASUME DICTAMEN PROVEEDOR $\leq 3$ (ppm)
PLOMO (USP)	CONFORME	$\leq 10$ (ppm)
PLOMO (Ph. Eur.)	CONFORME	SE ASUME DICTAMEN PROVEEDOR $\leq 10$ (ppm)
NIQUEL	CONFORME	SE ASUME DICTAMEN PROVEEDOR $\leq 5$ (ppm)
PERDIDA POR DESECACION	2.44	$\leq 6.0$ (%)
VALORACION (VOLUMETRICA)		
MAGNESIO	4.1	4.0 - 5.0 (SOBRE PRODUCTO SECO) (%)
<b>COMPOSICION ACIDOS GRASOS (CG)</b>		
ACIDO ESTEARICO	53.2	$\geq 40.0$ (%)
SUMA AC. ESTARICO Y PALMITICO	98.5	$\geq 90.0$ (%)
<b>CONTROL MICROBIOLOGICO</b>		
RECuento MICROBIOS AEROBIOS TOTALES 20		$\leq 1 \text{ E}3$ (ufc/g)
RECuento MOHOS Y LEVADURAS TOTALES <10		$\leq 1 \text{ E}2$ (ufc/g)
ESCHERICHIA COLI	CONFORME	AUSENCIA EN 1 g
SALMONELLA	CONFORME	AUSENCIA EN 10 g

Fecha análisis: 15-06-2010

Especificación: 3000169 ESTEARATO DE MAGNESIO (gen/ver: 13/1)

Dictamen: CONFORME

Nº Certificado: 703030933 / 1

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Cumple requerimientos de Ph. Eur. y USP

Certificado\_mmpc\_FISA\_mf.rep / 29091201

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## Annex 7. Certificate of Analysis of Meyprogat 90 (see table 1).



Ferrer Internacional S.A.  
Planta Especialidades Farmacéuticas  
Joan Buscà 1-8  
08173 Sant Cugat del Vallès  
Barcelona - España / Spain

**Certificado de análisis**

Producto:	MEYPROGAT 90		
Código producto:	3000293	Lote:	1E0398
Cantidad:	1175000,000 G	Proveedor:	SOBERAL S.L.
		Lote proveedor:	17171
		Fecha fabricación:	10-2008
		Fecha retest:	10-2011

Determinaciones	Resultado	Especificaciones
RECEPCION COA	CONFORME	CERTIFICADO RECEPCIONADO

Fecha análisis: 10-05-2011

Especificación: 3000293 MEYPROGAT 90 (V) (gar/ver: 2/1)

Dictamen: CONFORME

Responsable: Montse Planells

Certificado emitido electrónicamente, es válido sin firma

Cumple requerimientos de Ph. Eur.

Certificado\_mmpg\_FIA\_mt.rsp / 30101214

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Fecha impresión / Print date: 30-05-2011

May 03 2011 2:33PM GRUPO FERRER

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**DANISCO**

First you add knowledge ...

Report number: 13195  
800112081Danisco Zaanam B.V.  
P.O. Box 1106  
1506 AD Zaanam (NL)  
Dated: 155  
1502 BC Zaanam  
Phone: +31 (0)75 481 49 50  
Fax: +31 (0)75 435 43 62  
www.danisco.com  
info@danisco.comFerrer International  
C. / Joan Buscalla 1-9  
08190 SAN CUGAT DEL VALLES  
Spanien

21-Mar-11

## CERTIFICATE OF ANALYSIS

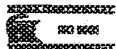
Product	:	MEYPROGAT
Type	:	90
Order no.	:	800112081
Control no.	:	17171
P.O.	:	PE000345
Prod. date	:	Oct-10
Expiry date	:	Oct-11

Moisture (%)	:	7,0
Viscosity 1% after full hydration (mPa.s)	:	674
pH	:	6,2
Mesh +M150 (%)	:	0,6
Ash content (%)	:	1,3
Plate count	:	900
Moulds	:	10
Yeast	:	<50
Coliforms	:	neg.

Comments: The above mentioned typical analyses  
meet our issued specifications.

Cc.: Food

Signature: VB

Danisco Zaanam B.V.  
Chamber of commerce  
File nr. 15067278

## Annex 8. Product request form for Sutrilneo 5 mg pills.

**ferrer** Departamento de Gestión Productos de Desarrollo CIDF 0425 (1)

**SOLICITUD / ENTREGA DE PRODUCTO**

Nº SOLICITUD  
(a rellenar por GPD)  
1110137

FECHA SOLICITUD	DEPARTAMENTO	SOLICITANTE	FIRMA
06 Oct. 11	ER-UAPA	JAUME SEUMA	

Código:	GF-009435-00
Producto:	SUTRILNEO (5mg)
Número de lote:	E009
Peso Neto / unidades:	2 comprimidos
Motivo:	Estudio nº: UAPA 10018-01
Otros:	
Observaciones:	Diferencia patente cristalinidad Tokasunida

Autorizado por:

Nombre	Firma	Fecha
Enrique A. Alab		4 Octubre 2011
Project Leader		

Documentación entregada con la sustancia:

	Cantidad Entregada
Certificado de análisis:	<input type="checkbox"/>
Ficha de seguridad:	<input type="checkbox"/>
Hoja de consumo de producto:	<input type="checkbox"/>
Otros (a especificar):	<input type="checkbox"/>

Entregado por:

Nombre	Firma	Fecha
Adrià Lozano		10/10/11
GPD		

Recibido por:

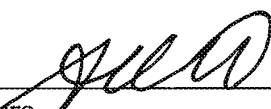
Nombre	Firma	Fecha
JAUME SEUMA		10 Oct. 11
Solicitante		

**COPIA AUTÉNTICA**  
Fecha: 10 Oct. 11  
Firma:

*Original in GPD*

Code: Sutrilneo 5 mg  
GF - 009435 - 00  
Batch: E009  
2 comprimidos

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

  
\_\_\_\_\_  
Signature

Dr. Antonio Guglietta  
\_\_\_\_\_  
Typed or Printed Name

Dec 16, 2011  
\_\_\_\_\_  
Date